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# Clinical Efficacy and Optimal Concentration of Ketotifen Ophthalmic on Allergic Conjunctivitis and Vernal Conjunctivitis

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Ketotifen ophthalmic (0.05% or 0.025%) was administered to 29 patients with allergic conjunctivitis, and its clinical effectiveness and optimal concentration were evaluated. With respect to global improvement, the improvement rate for the 0.05% preparation was higher than that for to 0.025% preparation: the former was 85% and the latter was 23%. No side effects and no abnormal laboratory findings were noted. The utility of the 0.05% preparation was thus higher than that of the 0.025% preparation ($p < 0.01$). These results confirm that 0.05% ketotifen ophthalmic is superior to 0.025% ketotifen ophthalmic.

Key words: Ketotifen ophthalmic; Allergic conjunctivitis; Vernel conjunctivitis, 0.05% vs 0.025% preparation

## Introduction

Ketotifen ophthalmic solution (HC ophthalmic solution) is an ophthalmic solution that has ketotifen (Figure 1) as the main ingredient. Ketotifen is expected to have a therapeutic effect in allergic conjunctivitis and vernal conjunctivitis if applied in the field of ophthalmology, because it has antiallergy action and antihistamine action [1-5].

As for the safety of HC ophthalmic solution, no particularly noteworthy effects on the outer ocular regions, anterior eye segment, or other ocular tissues were reported in concentrations up to 0.8% in a 13-week repeated instillation test using rabbits [6].

The safety of 0.05% and 0.1% HC ophthalmic solution was studed in a phase I trial in healthy adults [7]. As a result, 0.1% solution was judged to be undesirable in practice because there were many more complaints of transient "stinging" by 0.1% solution than by 0.05% solution. 0.05% solution was consequently selected as the clinical concentration.

As for the efficacy of HC ophthalmic solution, excellent results were reported by multicenter cooperative research on 0.05% HC ophthalmic solution in allergic conjunctivitis and vernal conjunctivitis [8]. On the other hand, the efficacy of HC ophthalmic solutions of concentrations lower than 0.05% has not been studied. The efficacy and safety of 0.05% and 0.025% HC ophthalmic solutions were therefore compared at Tokushima University and associated institutions and the results reported here.

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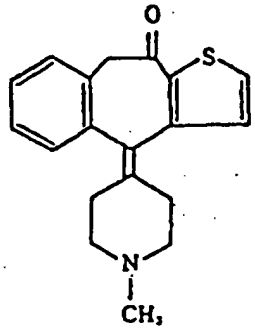


*Figure 1. Chemical structure of ketotifen.*

## I. Subjects and Trial Method

1. Subjects

Subjects among patients examined by the four institutions shown in Table 1 between August 1987 and April 1988 diagnosed with vernal conjunctivitis or allergic conjunctivitis in whom the participation of type I allergy had been confirmed by the eosinophil count in conjunctival scrapings, RAST IgE antibodies, and skin reactions served as the subjects. However, patients with other eye diseases (such as glaucoma, infectious conjunctivitis, and trachoma), contact lens wearers, patients who had undergone desensitization or modulation therapy within the last six months, pregnant women, nursing mothers, and women who might be pregnant, children less than 5 years of age, and subjects deemed inappropriate for incorporation in this trial by the attending physician were excluded as subjects.

Furthermore, administration of the ophthalmic solutions was begun after obtaining oral or written consent subsequent to an explanation of the nature of the trial, etc. to the patient or his or her family prior to beginning the trial.

| | | |
|---|---|---|
| Tokushima University | Department of Ophthalmology | Y. Nimura, Y. Fujita, Y. Inomoto |
| Tosa Shimin Hospital | Department of Ophthalmology | S. Miki |
| Kyosai Kumiai Shikoku Central Hospital | Department of Ophthalmology | T. Iwase |
| Kosciren Awa Hospital | Department of Ophthalmology | T. Kato |

*Table 1. Participating institutions.*

2. Trial drugs and allocation

0.05% HC ophthalmic solution (0.05% solution): colorless, transparent aqueous solution containing 0.5 mg of ketotifen per milliliter.

0.025% HC ophthalmic solution (0.025% solution): colorless, transparent aqueous solution containing 0.25 mg of ketotifen per milliliter.

As a general rule, the trial drugs (0.05% and 0.025% solutions) were allocated in alternation in the order in which the patients visited the hospital.

3. Administration method and duration

Following a from 3-day to 1-week preadministration observation period, the prescribed tests were conducted and the subject patients selected. The duration of treatment as a general rule was set at 4 weeks during which time the HC ophthalmic solution was instilled one or two drops at a time four times a day (morning, afternoon, evening, and before bed). When the condition was cured in less than 4 weeks, that point in time was taken as the end of the trial and the prescribed studies and evaluations conducted.

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4. Discontinuation of administration

The attending physician had the prerogative to discontinue instillation when grave side effects appeared, when abnormal clinical test values were discovered, or when the clinical symptoms and findings exacerbated. However, the prescribed studies and evaluations were to be conducted at the time of discontinuation when the trial was discontinued and the reasons for discontinuation and findings at the time of discontinuation, etc. were to be recorded on the case chart.

5. *Concomitant drugs*

All oral and ophthalmic drugs that might affect the evaluation of the efficacy of the trial drug such as antihistamines and antiallergy drugs other than the trial drug were prohibited during the trial. Use of steroids (oral and ophthalmic) from the preadministration observation period was allowed to continue only when their use was judged to be unavoidable given the severity of the symptoms. However, new steroid use and changes in method of use and dose were to be avoided during the trial. The patients were also instructed not to use any commercial eye drops they had on hand.

6. Studies and observation items

1) Patient background

Together with questioning the patients as to ocular diseases that complicated the allergic conjunctivitis or vernal conjunctivitis, systemic diseases, allergic rhinitis, atopic dermatitis, past history of asthma, disease form (seasonal or nonseasonal), usual time of onset, age at first onset, severity, and treatment up to the present time, the participation of type I allergy was to be confirmed by verifying the eosinophil count in conjunctival scrapings, RAST IgE antibodies in the serum, positive antigens by intracutaneous reaction and scratch reaction (using five types of antigens: mites, house dust, orchard grass dust, Japanese cedar pollen, and ragweed pollen), and measuring the blood eosinophils and serum IgE value whenever possible.

The eosinophil count in the conjunctival scrapings and skin reactions were evaluated according to the positivity criteria of Table 2.

| Test method \ Positivity | | +++ | ++ | + | - |
|---|---|---|---|---|---|
| Eosinophil count in discharge or conjunctival scraping | | Clusters | Between (+++) and (++) | Weak response | 0 |
| Skin reaction | Intracutaneous reaction | Erythema ≥41 mm<br>Wheals ≥15 mm | 40-21 mm<br>14-10 mm | 40-21 mm<br>≤9 mm | ≤20 mm<br>≤9 mm |
| | Scratch reaction | | | Erythema ≥15 mm<br>Wheals ≥5 mm | ≤14 mm<br>≤4 mm |

*Table 2. Criteria for evaluation of the eosinophil count in eye discharge or conjunctival scraping and the severity of skin reactions.*

2) Clinical symptoms

The following clinical symptoms were surveyed at the initial examination, at the beginning of the trial, 1, 2, 3, and 4 weeks after beginning the trial, and at the end of the trial. The severity was evaluated and recorded as severe (+++), moderate (++), mild (+), or none (-).

Ocular symptoms (subjective symptoms): pruritus, discharge, lacrimation, photophobia, feeling of a foreign object, eye pain.

Anterior segment findings (objective findings): congestion of the bulbar conjunctiva and chemosis, congestion, chemosis, follicles, and papillae of the palpebral conjunctiva, ulceration and erosion of the cornea, pathological changes in the ring.

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The patients were also given eye allergy journals and instructed to record the severity of the ocular symptoms (subjective symptoms) each day to serve as a reference in evaluating the symptoms.

3) Concomitant drugs

The name of the drug and dose (number of instillations, number of administrations and dose) were recorded when drugs other than HC ophthalmic solution were used.

4) Ophthalmological studies

The following studies were conducted whenever possible at the beginning and end of the trial: visual acuity, intraocular pressure, ophthalmoscopy, and slit lamp studies.

5) Clinical tests

The following tests were conducted whenever possible at the beginning and end of the trial.

Hematological studies: RBC, hemoglobin, hematocrit, WBC, leukocyte differential, platelet count.

Liver function tests: GOT, GPT, Al-P, bilirubin.

Kidney function tests: BUN, serum creatinine.

Urinalysis: glucose, protein, urobilinogen.

6) Side effects

The symptoms, severity, date of appearance, and causal relationship with the trial drug were to be studied when side effects appeared and the treatment of the side effects and subsequent course to be recorded concretely.

7. Clinical evaluation

1) Improvement divided by symptom

The improvement divided by symptom of each item was evaluated as [1] marked improvement, [2] improvement, [3] some improvement, [4] no change, [5] exacerbation, or [6] no symptom by comparing the severity of the symptom during the preadministration observation period with the severity of the symptom after 2 weeks of administration and at the end of the trial.

2) Global improvement

The global improvement was evaluated as [1] marked improvement, [2] improvement, [3] some improvement, [4] no change, [5] exacerbation, or [6] evaluation impossible by the attending physician by comparing the ocular symptoms and anterior segment findings at the end of the trial with those during the preadministration observation period.

3) Overall safety

The overall safety was evaluated as [1] safe (absolutely no side effects or abnormal clinical test values), [2] fairly safe (mild side effects or abnormal clinical test values [no treatment required]), [3] safety doubtful (moderate side effects or abnormal clinical test values [instillation continued with some type of treatment]), [4] not safe (severe side effects or abnormal clinical test values [instillation discontinued]), or [5] evaluation impossible by the attending physician by comprehensive consideration of the existence of side effects and changes in clinical test values at the end of the trial.

4) Utility

The utility was evaluated as [1] very useful, [2] useful, [3] fairly useful, [4] not particularly useful, [5] not useful, or [6] evaluation impossible by the attending physician by comprehensive consideration of the global improvement, overall safety, and patient background factors at the end of the trial.

## II. Trial Results

1. Patient background

Twenty-nine patients (0.05% solution: 14 subjects, 0.025% solution: 15 subjects) were administered HC ophthalmic solution during the trial. Table 3 shows the patient background. Table 4 shows a case summary. The majority of the 29 cases (26 cases, 90%) had allergic conjunctivitis. The disease form was nonseasonal and the severity was moderate in approximately half. The eosinophil count was at least (+) in the eye

(English translation / page 5)



discharge or conjunctival scrapings in 22 subjects (76%). Skin reactions and RAST were also positive in more than half.

Of the 29 subjects administered HC ophthalmic solution, one was excluded from the evaluation of efficacy for having other than the subject disease (phylctena) and two for inadequate washout of prior therapeutics (one administered 0.05% solution and one administered 0.025% solution). In cases that used steroid eye drops as prior treatment, one patient who switched the type of steroid eye drops at the beginning of instillation of the trial drug (0.05% solution) was used because steroid eye drops had been used before and after beginning instillation of the HC ophthalmic solution. Therefore, the efficacy was evaluated in 26 subjects (*0.05% solution: 13 cases and 0.025% solution: 13 cases*).

| | | HC ophthalmic solution concentration | | |
|---|---|---|---|---|
| | | 0.025% | 0.05% | Total |
| Sex | male<br>female | 8<br>7 | 3<br>11 | 11 (37.9%)<br>18 (62.1%) |
| Age | mean age (years) | 36.8 (5-72) | 22.4 (6-53) | 29.8 (5-72) |
| Diagnosis | allergic conjunctivitis<br>vernal conjunctivitis<br>other | 13<br>1<br>1 | 13<br>1<br>0 | 26 (89.7%)<br>2 (6.9%)<br>1 (3.4%) |
| Disease form | seasonal<br>nonseasonal<br>unknown | 2<br>9<br>4 | 5<br>5<br>4 | 7 (24.1%)<br>14 (48.3%)<br>8 (27.6%) |
| Severity | severe<br>moderate<br>mild | 1<br>8<br>6 | 1<br>10<br>3 | 2 (6.9%)<br>18 (62.1%)<br>9 (31.0%) |
| Allergy background | | | | |
| Eosinophil count in eye discharge or conjunctival scraping | +++<br>++<br>+<br>-<br>unknown | 0<br>4<br>8<br>2<br>1 | 1<br>5<br>4<br>4<br>0 | 1 (3.4%)<br>9 (31.0%)<br>12 (41.4%)<br>6 (20.7%)<br>1 (3.4%) |
| Skin reaction (intracutaneous reaction or scratch reaction) | positive<br>negative<br>unknown | 5<br>2<br>8 | 11<br>0<br>3 | 16 (55.2%)<br>2 (6.9%)<br>11 (37.9%) |
| RAST | positive<br>negative<br>unknown | 6<br>8<br>1 | 11<br>3<br>0 | 17 (58.6%)<br>11 (37.9%)<br>1 (3.4) |

*Table 3. Patient background.*

(English translation / page 6)



| Case No. | Patient, Sex, Age | Diagnosis | Disease form | Severity | Complications, atopic disease | Allergy background | | Prior treatment (duration) | Duration of HC administration (W) | Concomitant drugs (duration) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Urticaria/dilis | RAST, intracutaneous reaction, scratch reaction | | | |
| 1 | M.T. male 9 | Allergic conjunctivitis | Nonseasonal | Mild | Eye: accommodative strain | ++ | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | 1/2: Cinalbon eye drops, 1W<br>1/2: Kinkamin eye drops, 1W | 4W | |
| 2 | O.H. female 46 | Phylcena | Nonseasonal | Mild | | - | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | | 4W | Kinkamin A eye drops, 1W |
| 3 | E.M. female 61 | Allergic conjunctivitis | Nonseasonal | Mild | Atopic dermatitis | + | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | 1/2: Kinkamin eye drops, 1W | 4W | |
| 4 | M.Y. male 59 | Allergic conjunctivitis | Unknown | Mild | Eye: retinal vein hemorrhage, occlusion<br>Systemic: hypertension | ++ | | | 4W | |
| 5 | N.T. female 62 | Allergic conjunctivitis | Nonseasonal | Mild | Systemic: hepatitis | + | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | Sofradex eye drops, 1W | 4W | |
| 6 | O.S. female 14 | Allergic conjunctivitis | Seasonal | Mild | Allergic rhinitis | ++ | RAST: orchard grass (++), Japanese cedar (++), ragweed (++), III (++)<br>Intracutaneous reaction: orchard grass (++), Japanese cedar (++), ragweed (++), III (++) | | 4W | |
| 7 | I.S. female 40 | Allergic conjunctivitis | Seasonal | Moderate | | + | RAST: mites (+), orchard grass (+), Japanese cedar (++), ragweed (++), III (+)<br>Scratch test: orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | | 4W | |
| 8 | S.H. male 16 | Allergic conjunctivitis | Unknown | Moderate | Systemic: myocarditis<br>Allergic rhinitis | + | RAST: mites (++), orchard grass (+), Japanese cedar (+), ragweed (+), III (+)<br>Intracutaneous reaction: orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | | 4W | |

*Table 4-1. Summary of cases administered HC ophthalmic solution (1).*

0.025%

| Case No. | Ocular symptoms | | | | | | Bulbar | | Palpebral | | Overall evaluation | | | Side effects and abnormal clinical test values | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pruritus | Discharge | Lacrimation | Photophobia | Feeling of foreign object | Eye pain | Congestion | Chemosis | Congestion | Chemosis | Global improvement | Overall safety | Utility | | |
| 1 | improvement | | | | | | improvement | | improvement | | improvement | safe | useful | none | Rinderon eye drops, IW washout |
| 2 | | | | | improvement | | improvement | | | | improvement | safe | somewhat useful | none | Excluded from evaluation of efficacy for having other than subject disease |
| 3 | some improvement | | | | some improvement | improvement | | | exacerbation | exacerbation | exacerbation | safe | not particularly useful | none | Excluded from evaluation of efficacy for no washout of prior therapeutics |
| 4 | improvement | | | | improvement | | some improvement | | exacerbation | | some improvement | safe | somewhat useful | none | |
| 5 | no change | no change | | | | | | | | | no change | safe | somewhat useful | none | |
| 6 | improvement | some improvement | | | some improvement | | no change | some improvement | no change | no change | some improvement | safe | useful | none | |
| 7 | some improvement | some improvement | no change | no change | no change | | some improvement | no change | some improvement | no change | some improvement | safe | not particularly useful | none | |
| 8 | no change | | some improvement | | | exacerbation | no change | no change | no change | no change | no change | safe | not useful | none | |

*Table 4-1. Summary of cases administered HC ophthalmic solution (1).*

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0.025%

| Case No. | Patient, Sex, Age | Diagnosis | Disease form | Severity | Complications, atopic disease | Allergy background | | Other treatment (duration) | Duration of HC administration (W) | Concomitant drugs (duration) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Eosinophils | RAST, intracutaneous reaction, scratch reaction | | | |
| 9 | H.M. female 68 | Allergic conjunctivitis | Nonseasonal | Moderate | | ++ | RAST: mites (++++), orchard grass (+), Japanese cedar (+), ragweed (+), III) (+++) | | 4W | |
| 10 | K.M. male 71 | Allergic conjunctivitis | Unknown | Moderate | | + | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III) (+) Scratch test: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III) (+) | | 5W | |
| 11 | K.K. female 72 | Allergic conjunctivitis | Nonseasonal | Moderate | | + | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III) (+) Scratch test: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III) (+) | | 4W | |
| 12 | M.T. male 9 | Allergic conjunctivitis | Nonseasonal | Severe | Atopic dermatitis | | RAST: mites (++++), orchard grass (+), Japanese cedar (+), ragweed (+), III) (++++) | | 4W | |
| 13 | H.S. male 11 | Allergic conjunctivitis | Nonseasonal | Moderate | | - | RAST: mites (++++), orchard grass (+), Japanese cedar (+), ragweed (+), III) (++) | | 4W | |
| 14 | Y.Y. male 5 | Allergic conjunctivitis | Nonseasonal | Moderate | Allergic rhinitis | + | RAST: mites (+), orchard grass (+) Japanese cedar (+), ragweed (+), III) (+) Intracutaneous reaction: orchard grass (+), Japanese cedar (+), ragweed (+), III) (+) | | 6W | |
| 15 | S.H. male 9 | Vernal conjunctivitis | Unknown | Moderate | Allergic rhinitis | + | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III) (+) Intracutaneous reaction: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+) | | 4W | |

*Table 4-1. Summary of cases administered HC ophthalmic solution (2).*

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0.05%

| Case No. | Patient, Sex, Age | Diagnosis | Disease form | Severity | Diagnosis [sic] | Allergy background | | Prior treatment (duration) | Duration of HC administration (W) | Concomitant drugs (duration) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Eosinophils | RAST, intracutaneous reaction, scratch reaction | | | |
| 1 | O.R. male 6 | Allergic conjunctivitis | Nonseasonal | Moderate | Atopic dermatitis | + | RAST: mites (+++), orchard grass (+), Japanese cedar (-), ragweed (-), III (+++) | | 4W | |
| 2 | L.Y. female 53 | Allergic conjunctivitis | Nonseasonal | Moderate | | - | RAST: mites (+++), orchard grass (+), Japanese cedar (+++), ragweed (-), III (+++) | | 4W | |
| 3 | S.S. female 52 | Allergic conjunctivitis | Nonseasonal | Moderate | | + | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (-), III (-)<br>Intracutaneous reaction: mites (+), orchard grass (+), Japanese cedar (+), ragweed (+), III (+) | | 4W | |
| 4 | H.K. female 12 | Allergic conjunctivitis | Unknown | Moderate | Cyc. myopia<br>Systemic atopic dermatitis | ++ | RAST: mites (+++), orchard grass (+++), Japanese cedar (+++), ragweed (+++), III (+++)<br>Intracutaneous reaction: orchard grass (+++), Japanese cedar (+++), ragweed (+++), III (+++) | | 4W | |
| 5 | S.M. female 13 | Allergic conjunctivitis | Seasonal | Moderate | | - | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (-), III (-)<br>Intracutaneous reaction: orchard grass (+), Japanese cedar (+), ragweed (++), III (++) | | 4W | |
| 6 | O.M. female 32 | Allergic conjunctivitis | Seasonal | Mild | Allergic rhinitis | - | RAST: mites (+), orchard grass (+), Japanese cedar (+), ragweed (-), III (-)<br>Intracutaneous reaction: orchard grass (+), Japanese cedar (+), ragweed (+), III (++) | | 4W | |
| 7 | N.M. female 39 | Allergic conjunctivitis | Nonseasonal | Moderate | | - | RAST: mites (+++), orchard grass (+++), Japanese cedar (+++), ragweed (+++), III (+++)<br>Intracutaneous reaction: orchard grass (+++), Japanese cedar (+++), ragweed (+++), III (+++) | | 4W | |

*Table 4-2. Summary of cases administered HC ophthalmic solution (1).*

0.05%

| Case No. | Ocular symptoms | | | | | | Bulbar | | Palpebral | | Overall evaluation | | | Side effects and abnormal clinical test values | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pruritus | Discharge | Lacrimation | Photophobia | Feeling of foreign object | Eye pain | Congestion | Chemosis | Congestion | Chemosis | Global improvement | Overall safety | Utility | | |
| 1 | improvement | | no change | | | | improvement | improvement | | improvement | improvement | safe | useful | none | |
| 2 | improvement | | | | | | improvement | improvement | improvement | improvement | improvement | safe | useful | none | |
| 3 | | | | marked improvement | improvement | | improvement | improvement | improvement | improvement | improvement | safe | useful | none | |
| 4 | no change | | | | marked improvement | marked improvement | improvement | improvement | marked improvement | marked improvement | marked improvement | safe | useful | none | |
| 5 | marked improvement | | improvement | improvement | marked improvement | improvement | improvement | no change | marked improvement | improvement | marked improvement | safe | useful | none | |
| 6 | improvement | | some improvement | improvement | improvement | | some improvement | improvement | improvement | improvement | some improvement | safe | useful | none | |
| 7 | marked improvement | improvement | | improvement | no change | | some improvement | marked improvement | marked improvement | marked improvement | improvement | safe | useful | none | |

*Table 4-3. Summary of cases administered HC ophthalmic solution (1).*

0.05%

| Case No. | Patient, Sex, Age | Diagnosis | Disease form | Severity | Complications, atopic disease | Allergy background | | Prior treatment (duration) | Duration of HC administration (W) | Concomitant drugs (duration) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Eosinophils | RAST, intracutaneous reaction, scratch reaction | | | |
| 8 | M.S. female 11 | Vernal conjunctivitis | Seasonal | Severe | Allergic rhinitis, atopic dermatitis, asthma | +++ | RAST: mites (+++), orchard grass (+), Japanese cedar (++), HD (+++) | 0.1% Flumetholon, 1W<br>Tobracin, 1W | 4W | Salpevin eye drops, 4W<br>Rinderon A ointment<br>0.1% Rinderon eye drops, 4W |
| 9 | I.M. female 12 | Allergic conjunctivitis | Unknown | Moderate | | + | RAST: mites (-), orchard grass (+++), Japanese cedar (-), ragweed (-), HD (-)<br>Intracutaneous reaction: orchard grass (-), Japanese cedar (-), ragweed (-), HD (+) | | 4W | |
| 10 | N.T. female 35 | Allergic conjunctivitis | Seasonal | Mild | Allergic rhinitis, asthma | ++ | RAST: mites (++), orchard grass (++++), Japanese cedar (+++), ragweed (+), HD (++)<br>Intracutaneous reaction: orchard grass (++), Japanese cedar (+), ragweed (++), HD (+) | | 4W | |
| 11 | S.H. male 16 | Allergic conjunctivitis | Unknown | Moderate | Systemic: myocarditis | + | RAST: mites (+++), orchard grass (-), Japanese cedar (-), ragweed (-), HD (+++)<br>Intracutaneous reaction: orchard grass (-), Japanese cedar (+), ragweed (-), HD (++) | 0.025% HC ophthalmic solution, 1W | 1W | |
| 12 | O.T. female 9 | Allergic conjunctivitis | Seasonal | Moderate | Allergic rhinitis | ++ | RAST: mites (++++), orchard grass (-), Japanese cedar (-), ragweed (-), HD (++)<br>Intracutaneous reaction: orchard grass (-), Japanese cedar (-), ragweed (-), HD (++) | | 4W | |
| 13 | Y.T. female 14 | Allergic conjunctivitis | Nonseasonal | Mild | Atopic dermatitis | ++ | RAST: mites (+++), orchard grass (-), Japanese cedar (-), ragweed (+), HD (-)<br>Intracutaneous reaction: orchard grass (-), Japanese cedar (-), ragweed (-), HD (+) | | 4W | |
| 14 | O.M. male 9 | Allergic conjunctivitis | Unknown | Moderate | | ++ | RAST: mites (++++), orchard grass (-), Japanese cedar (+++), ragweed (-), HD (+++)<br>Intracutaneous reaction: orchard grass (-), Japanese cedar (-), ragweed (-), HD (+) | | 5W | |

*Table 4-2. Summary of cases administered HC ophthalmic solution (2).*

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0.05%

| Case No. | Ocular symptoms | | | | | | Objective | | Subjective | | Overall evaluation | | | Side effects and abnormal clinical test values | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pruritus | Discharge | Lacrimation | Photophobia | Feeling of foreign object | Eye pain | Congestion | Chemosis | Congestion | Chemosis | Clinical improvement | Overall safety | Utility | | |
| 8 | improvement | improvement | improvement | improvement | improvement | improvement | some improvement | no change | some improvement | some improvement | some improvement | safe | fairly useful | none | Steroids switched at the beginning of the medication |
| 9 | some improvement | | | some improvement | | | some improvement | some improvement | some improvement | some improvement | improvement | safe | useful | none | |
| 10 | improvement | some improvement | some improvement | | improvement | | some improvement | some improvement | some improvement | some improvement | marked improvement | safe | very useful | none | |
| 11 | some improvement | | some improvement | | | | no change | no change | no change | no change | improvement | safe | useful | none | Unchanged from evaluation of efficacy for washout of prior therapeutics |
| 12 | some improvement | no change | some improvement | | | | some improvement | some improvement | some improvement | some improvement | improvement | safe | useful | none | |
| 13 | some improvement | | | | | some improvement | some improvement | some improvement | no change | no change | improvement | safe | useful | none | |
| 14 | some improvement | no change | | | some improvement | | improvement | some improvement | no change | no change | improvement | safe | useful | none | |

Table 4-2. Summary of cases administered IIC ophthalmic solution (2).

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2. Global improvement

Table 5 shows the gobal improvement by the two solutions. While the percentage evaluated as at least improved was 85% by 0.05% solution, it was 23% by 0.025% solution, giving the 0.05% solution a significantly higher improvement rate ($p < 0.01$, U-test and $\chi 2$-test).

| Drug concentration | Marked improvement | Improvement | Slight improvement | No change | Exacerbation | Total | At least improved (%) | Test | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | U-test | $\chi^2$-test |
| 0.025% | 0 | 3 | 6 | 4 | 0 | 13 | 23.1 | p<0.01 | p<0.01 |
| 0.05% | 3 | 8 | 2 | 0 | 0 | 13 | 84.6 | | |

*Table 5. Global improvement.*

3. Improvement divided by symptoms

An examination of the improvement of the subjective symptoms at the end of the trial (Table 6) showed high improvement rates in both eyes for pruritus, photophobia, and feeling of a foreign object which are characteristic subjective symptoms in allergic conjunctivitis. However, the improvement rates were 8 to 13% higher by 0.05% solution than 0.025% solution. While the improvement rate of eye pain was 75% by 0.05% solution, that by 0.025% solution was low at 33%. An examination of the improvement of the objective findings (Table 7) shows an improvement rate (at least improvement) of bulbar conjunctival congestion of 46% by 0.05% solution (at least some improvement: 100%, the same below) in contrast to 25% (42%) by 0.025% solution. The improvement rate by 0.05% solution was thus significantly higher ($p < 0.05$, U-test). The improvement rate of bulbar chemosis as well was 46% (85%) by 0.05% solution as opposed to 29% (43%) by 0.025% solution. In palpebral conjunctiva congestion and chemosis as well, 0.05% solution gave significantly higher improvement rates than 0.025% solution. Neither solution produced marked improvement of palpebral conjunctiva follicles, papillae, or changes in the ring.

| Symptoms | Drug concentration (%) | Improvement divided by symptom | | | | | | | Test | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Marked Improvement | Improvement | Some improvement | No change | Exacerbation | Total | At least improved (%) | U-test | $\chi^2$-test (at least improved) |
| Pruritus | 0.025<br>0.05 | 1<br>2 | 4<br>5 | 3<br>4 | 2<br>1 | 0<br>0 | 10<br>12 | 50.0<br>58.3 | NS | NS |
| Discharge | 0.025<br>0.05 | 1<br>0 | 1<br>2 | 3<br>1 | 2<br>2 | 0<br>0 | 7<br>5 | 28.6<br>40.0 | NS | NS |
| Lacrimation | 0.025<br>0.05 | 1<br>0 | 1<br>2 | 2<br>3 | 3<br>1 | 0<br>0 | 7<br>6 | 28.6<br>33.3 | NS | NS |
| Photophobia | 0.025<br>0.05 | 1<br>1 | 2<br>4 | 0<br>1 | 1<br>0 | 0<br>0 | 4<br>6 | 75.0<br>83.3 | NS | NS |
| Feeling of foreign object | 0.025<br>0.05 | 0<br>2 | 5<br>4 | 1<br>1 | 2<br>1 | 0<br>0 | 8<br>8 | 62.5<br>75.0 | NS | NS |
| Eye pain | 0.025<br>0.05 | 0<br>1 | 2<br>2 | 1<br>1 | 2<br>0 | 2<br>0 | 6<br>4 | 33.3<br>75.0 | NS | NS |

*Table 6. Improvement of subjective symptoms by HC ophthalmic solution.*

(English translation / page 14)



| Symptoms | Drug concentration (%) | Improvement divided by symptom | | | | | | | Test | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Marked improvement | Improvement | Some improvement | No change | Exacerbation | Total | At least improved (%) / at least some improvement | U-test | χ²-test / at least improved |
| Bulbar conjunctiva | | | | | | | | | | |
| Congestion | 0.025<br>0.05 | 1<br>0 | 2<br>6 | 2<br>7 | 7<br>0 | 0<br>0 | 12<br>13 | 25.0 (41.6)<br>46.2 (100) | p < 0.05 | NS |
| Chemosis | 0.025<br>0.05 | 1<br>1 | 1<br>5 | 1<br>5 | 4<br>2 | 0<br>0 | 7<br>13 | 28.6 (42.9)<br>46.2 (84.6) | NS | NS |
| Palpebral conjunctiva | | | | | | | | | | |
| Congestion | 0.025<br>0.05 | 0<br>3 | 1<br>3 | 2<br>4 | 7<br>2 | 1<br>0 | 12<br>12 | 16.7 (33.3)<br>50.0 (83.3) | p < 0.05 | NS |
| Chemosis | 0.025<br>0.05 | 0<br>2 | 1<br>5 | 0<br>4 | 6<br>2 | 0<br>0 | 7<br>13 | 14.3 (14.3)<br>53.8 (84.6) | p < 0.01 | NS |
| Follicles | 0.025<br>0.05 | 0<br>0 | 0<br>0 | 5<br>6 | 6<br>5 | 0<br>0 | 11<br>11 | 0 (45.5)<br>0 (54.5) | NS | NS |
| Papillae | 0.025<br>0.05 | 0<br>0 | 0<br>0 | 2<br>3 | 1<br>2 | 0<br>0 | 3<br>5 | 0 (66.7)<br>0 (60.0) | NS | NS |
| Cornea | | | | | | | | | | |
| Ulceration | 0.025<br>0.05 | 0<br>0 | 0<br>0 | 0<br>1 | 0<br>0 | 0<br>0 | 0<br>1 | 0 (100) | - | - |
| Erosion | 0.025<br>0.05 | 0<br>0 | 0<br>0 | 0<br>0 | 0<br>2 | 0<br>0 | 0<br>2 | 0 (0) | - | - |
| Ring | 0.025<br>0.05 | 0<br>0 | 1<br>0 | 0<br>1 | 4<br>3 | 0<br>1 | 5<br>5 | 20.0 (20.0)<br>0 (20.0) | NS | NS |

*Table 7. Improvement of objective findings by HC ophthalmic solution.*

4. Overall safety

None of the 29 subjects (0.05% solution: 14 cases and 0.025% solution: 15 cases) administered HC ophthalmic solution presented any side effects or abnormal clinical test values during the trial. The overall safety that considered the side effects and abnormal clinical test values was judged to be "safe" in all cases.

5. Utility

Table 8 shows the evaluation of utility by the attending physician by considering the global improvement, overall safety, and patient background factors. While 0.05% solution was found to be at least useful in 12 subjects (92%), 0.025% solution was only at least useful in four (31%). There was thus a significant difference between the 0.05% and 0.025% solutions ($p < 0.01$, U-test and $\chi 2$-test).

(English translation / page 15)



| Drug concentration (%) | Very useful | Useful | Somewhat useful | Not particularly useful | Not useful | Total | At least useful (%) | Test | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | U-test | $\chi^2$-test |
| 0.025 | 0 | 4 | 5 | 2 | 2 | 13 | 30.8 | $p < 0.01$ | $p < 0.01$ |
| 0.05 | 1 | 11 | 1 | 0 | 0 | 13 | 92.3 | | |

*Table 8. Utility.*

## III. Discussion

Ketotifen ophthalmic solution (HC ophthalmic solution) is reported to dose-dependently suppress conjunctivitis in experimental allergic conjunctivitis models [9]. It is of great interest whether or not the dose dependence evidenced in animal experiments is reflected in clinical application. The efficacy and safety were compared here by administering 0.05% and 0.025% HC ophthalmic solutions four times a day for 4 weeks to patients with allergic conjunctivitis and vernal conjunctivitis in which the participation of type I allergy had been confirmed.

While the efficacy expressed by the global improvement rate showed an efficacy rate (at least improved) of 85% by 0.05% solution, the rate was only 23% by 0.025% solution. 0.05% solution was thus significantly superior. An investigation as the improvement of the subjective symptoms found both solutions to give high efficacy rates in pruritus, photophobia, and feeling of a foreign object. However, 0.05% solution gave 8 to 13% higher improvement rates than 0.025% solution. An examination of the improvement of the objective symptoms found the improvement rate in conjunctival congestion to be 46% (bulbar) and 50% (palpebral) by 0.05% solution in contrast to 25% (bulbar) and 17% (palpebral) by 0.025% solution. 0.05% solution thus gave significantly higher improvement rates. The rates of improvement of chemosis as well were higher by 0.05% solution with 46% (bulbar) and 54% (palpebral) by 0.05% solution in comparison to 29% (bulbar) and 14% (palpebral) by 0.025% solution. It is assumed that in the final analysis the differences in the improvement rates of bulbar and palpebral conjunctiva congestion and chemosis by 0.05% and 0.025% solution produced the difference in the evaluation of global improvement. On the other hand, improvement of palpebral conjunctival follicles, papillae, and pathological changes in the ring was very low by both solutions. Similar results are reported for another antiallergy drug, disodium cromoglycate [10]. A satisfactory therapeutic effect is probably not obtained in follicles, papillae, and changes in the ring with short term trials of only 4 weeks.

As for the safety, there were no side effects or abnormal clinical test values at all during the trial. HC ophthalmic solution can be called a relatively safe ophthalmic solution because the overall safety was judged to be good in all cases.

To summarize the above, a comparison of the efficacy and safety of 0.05% HC ophthalmic solution and 0.025% HC ophthalmic solution showed 0.05% solution to be better than 0.025% solution in terms of efficacy. As for safety, no side effects or abnormal clinical test values were found in either group. Although it is difficult to draw a conclusion from the present results because only 30 cases were studied here in the two groups combined, the results generally appear to indicate that 0.05% HC ophthalmic solution is superior to 0.025% HC ophthalmic solution.

(English translation / page 16)



## Summary

(1) The efficacy and safety were compared by using ketotifen ophthalmic solutions (0.05% and 0.025% solutions) in 29 patients with allergic conjunctivitis and vernal conjunctivitis.

(2) In the global improvement, 85% of those administered 0.05% solution were evaluated as at least improved in comparison to 23% by 0.025% solution. 0.05% solution thus gave a significantly higher improvement rate.

(3) There were no side effects or abnormal clinical test values at all in either group during the trial.

(4) The evaluation of utility based comprehensively on efficacy and safety was significantly higher by 0.05% solution than 0.025% solution. 0.05% solution is therefore believed to be superior to 0.025% solution.

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